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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/553,118

11/03/2005

Takashi Shinohara

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EXAMINER

TON, THAIAN N

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/553,118	Applicant(s) SHINOHARA ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 13-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/23/11</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-27 are pending; claims 13-27 are withdrawn; claims 1-12 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 10/23/07 and 1/11/06 have been considered.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-12) in the reply filed on 2/6/08 is acknowledged. The traversal is on the ground(s) that the claims in Groups I and IV-VIII are linked so as to share at least one common special technical feature, namely that they recite culturing spermatogonial stem cells in a medium containing GDNF and LIF, and that this special technical feature defines the contribution that each claim makes over the prior art (see p. 2 of the Response). Applicants argue that additionally, a search for prior art with respect to any of Groups I and IV-VIII would likely uncover references that would be considered by the Examiner during the examination of other groups, and that there would be no undue burden in examining the claims of Groups I and IV-VIII at the same time. Applicants cite MPEP §803.

This is not found persuasive because the instant case is a 371, where burden is not a requirement. See also, MPEP §801, which explicitly states that, "applications entering the National Stage under 35 U.S.C. 371 as a Designated or Elected Office in the U.S. Patent and Trademark Office is covered in Chapter 1800." Wherein Chapter 1800, and specifically, 1893.03 (d), clearly states that, "Examiners are reminded that unity of invention (not restriction) practice is applicable in international applications (both Chapter

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I and II) and in national stage applications submitted under 35 U.S.C. 371.” (emphasis added).

Thus, the Examiner has shown that Groups I and IV-VIII designated in the Restriction requirement, mailed 1/11/08 do not relate to a single general inventive concept under PCT Rule 13.1. The Examiner has clearly delineated the first product and other categories related thereto. See page 4 of the Restriction requirement. Additionally, unity of invention does not allow for multiple products, methods of using or making said products (see p. 3 of the Restriction requirement). Therefore, the additional, non elected groups are directed to different categories of invention that fail to have unity, as defined by PCT, Rule 13.2.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/6/08.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by Nagano *et al.* (Biol. Reprod., 68: 2207-2214, 2003, IDS).

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Claim 12 is considered a product-by-process claim. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Nagano teach spermatogonial stem cells (SSC).

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Nagano *et al.* (**Tissue & Cell**, 30(4): 389-397, 1998, IDS).

Nagano teach spermatogonial stem cells. See Abstract. Accordingly, they anticipate the claimed invention.

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Nagano *et al.* (**PNAS**, 68(23): 13090-13095, November 6, 2001, IDS).

Claim 12 is considered a product-by-process claim (see above). Nagano teach spermatogonial stem cells (p. 13092, 1st col.).

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Claims 1-3, 5, 6 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Creemers *et al.* (**Reproduction**, 124: 791-799, 2002) as evidenced by Human embryology, Embryogenesis(<http://www.embryology.ch/anglais/cgametogen/spermato03.html>, accessed online on May 15, 2008)

Regarding claims 1, 2, and 12, Creemers teach culturing type A spermatogonial in KSOM medium containing LIF, bFGF, and additionally, GDNF (p. 793, col. 1).

Regarding claim 3, Creemers teach that the medium contains 2.5% fetal calf serum (, p. 793, col. 1, 1st ¶ and Figure 5).

Regarding claim 5, Creemers teach isolating type A spermatogonial from mice (p. 792, col. 2, Animals).

Regarding claim 6, Creemers teach that the GDNF concentration was 2, 10, 24 ng/ml (p. 793, col. 1, 1st ¶).

Human embryology, Embryogenesis website provide evidence to show that type A spermatogonia contain stem cells (see pages 1-2, Figure 12, Legend).

Accordingly, Creemers anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7, 9, 11, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.* (**Reproduction**, 124: 791-799, 2002) as

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evidenced by Human embryology, Embryogenesis

(<http://www.embryology.ch/anglais/cgametogen/spermato03.html>, accessed online on May 15, 2008) when taken with Nagano *et al.* (**Biol. Reprod.**, 68: 2207-2214, 2003, IDS).

Creemers teach culturing type A spermatogonial in KSOM medium containing LIF, bFGF, and additionally, GDNF (p. 793, col. 1). They teach that the medium contains 2.5% fetal calf serum (, p. 793, col. 1, 1st ¶ and Figure 5). Creemers teach isolating type A spermatogonial from mice (p. 792, col. 2, Animals). Creemers teach that the GDNF concentration was 2, 10, 24 ng/ml (p. 793, col. 1, 1st ¶). The Human embryology, Embryogenesis website provide evidence to show that type A spermatogonia contain stem cells (see pages 1-2, Figure 12, Legend).

Creemers do not specifically teach the specific concentrations of LIF or bFGF required by claims 7 and 9.

Although Creemers does not specifically teach that the concentration of LIF is 102 to 104 units/ml and that bFGF is at 0.5 to 50 ng/ml, it would have been obvious for one ordinarily skilled in the art to perform routine optimization of culture conditions of spermatogonial stem cells. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific concentrations of LIF and bFGF in the culture medium was other than routine, that the medium resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Creemers do not specifically teach growing spermatogonial stem cells on feeder cells (claim 4). However, prior to the time of filing, Nagano teach

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culturing spermatogonial stem cells (SSC) with feeder cells (p. 2208, col. 1, Donor Mice and Cell Culture, 2nd ¶) and show an increase in SSC maintenance using OP9 and L cells after 7 days of culture (see Figure 1 and p. 2212, 1st full ¶).

Accordingly, in view of the combined teachings, one of ordinary skill in the art would have been motivated to modify the culture techniques of Creemers to include feeder layers, such as the OP9 and L feeder layers taught by Nagano, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to use a feeder layer because of the increase in efficiency of SSC maintenance using these cell lines.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 5-9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.* (above) as evidenced by Human embryology, Embryogenesis (above) when taken with Wahab-Wahlgren (**Mol. And Cell. Endocrin.**, 201: 39-46, March 28, 2003) in further view of Haneji *et al.* (**J. Endocrin.**, 128: 383-388, 1991).

Creemers is summarized above. They do not specifically teach culturing the spermatogonial cells on feeder cells (claims 4 and 11) or that EGF is used in the medium (claims 2 and 8). However, prior to the time of filing, Wahab-Wahlgren teach that EGF plays an important role in spermatogonial proliferation *in vitro* (see Abstract and p. 44, col. 1, Discussion, first ¶). Haneji teach that EGF inhibits the differentiation of type A spermatogonia (p. 385, col. 1, and Figure 2). Additionally, Haneji teach using varying concentration of EGF from 0.1-500 ng/ml.

Accordingly, it would have been obvious to one of ordinary skill in the art to modify the techniques of culturing spermatogonial cells, as taught by Creemers, to include EGF, as taught by Wahab-Wahlgren and Haneji, with a

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reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification because of the observation that EGF inhibits the differentiation of sperm stem cells. Thus, one of skill in the art would use EGF in order to maintain the spermatogonial stem cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 5-7, 9, 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.* (above) as evidenced by Human embryology, Embryogenesis (above) when taken with Izadyar *et al.* (Biol. Reprod., 68: 272-281, 2003, IDS).

Creemers is summarized above. They do not specifically teach that the serum is contained at a concentration of 0.1 to 5% in the medium at the start of cultivation and then at a concentration of 0.1 to 20% in the medium after passage of the spermatogonial stem cells. Although Creemers teach utilizing 2.5% serum, they do not teach a change in this concentration. However, prior to the time of the claimed invention, Izadyar teach cultivation of bovine type A spermatogonial, which contain spermatogonial stem cells (p. 272, col. 2, 1st full ¶) and evaluate the effects and show that an increase in the amount of serum results in the increase in the proliferation activity of bovine type A spermatogonial (Figure 1).

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to modify the teachings of Creemers to increase the amount of serum amount after passage in order to increase the proliferation activity, with a reasonable expectation of success. This modification would have been wholly within the skill of the ordinary artisan, and the ordinary artisan would have been motivated to make this modification in order to increase the number of proliferating type A spermatogonia, including sperm stem cells.

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Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/

Primary Examiner, Art Unit 1632